Relationships between Auditory Event-Related Potentials and Mood State, Medication, and Comorbid Psychiatric Illness in Patients with Bipolar Disorder

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Abstract

Background—Patients with bipolar disorder (BD) exhibit aberrations in auditory event-related potentials (ERPs), although the relationship between these measures and mood state at testing, comorbid psychiatric illness, presence of psychotic features, and medication usage are unclear. The purpose of this study was to investigate the relationships between these factors and auditory ERP measures in BD patients.

Methods—An auditory “oddball” discrimination task was used to elicit ERPs from sixty-nine patients with type I BD and 52 healthy controls. Patients were placed into subgroups based upon their mood state at testing (euthymic or symptomatic), and ANOVA was used to compare amplitude and peak latency measures from the N100, P200, N200, and P300 ERP components across subgroups. Multiple regression was used to investigate relationships between ERP measures and comorbid psychiatric diagnosis, history of psychotic features, and medication status.

Results—Relative to healthy control participants, euthymic and symptomatic BD patients exhibited reduced P300 and P200 amplitude, but ERP measures did not differ among BD patients on the basis of mood status. A history of a comorbid anxiety disorder was associated with reduced N200 peak latency, but prolonged P300 peak latency among BD patients. No other relationships between clinical variables and ERP measures were significant.
Conclusions—The results suggest that disrupted auditory attention may be observed in BD patients regardless of their mood state at testing, medication status, or history of psychosis. These results extend previous findings, and provide further evidence for aberrations in the P300 ERP as an endophenotype for BD.

Keywords
Event-related potentials; P300; Bipolar Disorder

Previous research has demonstrated that individuals with bipolar disorder (BD) differ from healthy comparison subjects on event-related potential (ERP) measures of auditory processing elicited during “oddball” discrimination tasks. In these tasks, participants must identify infrequent, target tones presented within a series of frequent, distracter tones. Frequent tones elicit the N100 and P200 ERP components, whereas target tones elicit those components as well as the N200 and P300 ERPs. Studies of ERPs in BD have focused on the P300, which is a positive-going wave that peaks approximately 300 ms after the presentation of a target tone and is believed to provide an index of selective attention and general cognitive efficiency (1). The peak latency of this component is believed to index stimulus evaluation speed independent of reaction time (2), whereas its amplitude may represent neural activity underlying attention and memory processes involved in updating stimulus representations (1, 3). Aberrations in auditory ERPs may reflect a neurophysiological marker, or endophenotype, for BD (4–6) but the effects of patients’ mood state, current medication usage, or history of other psychiatric disorders on these measures are not well understood. Therefore, the purpose of the present investigation was to extend the results of previous studies by examining the relationship between active mood symptoms, history of an anxiety or substance-use disorder, medication status, and history of psychotic features on the P300 and earlier auditory ERPs (N100, P200, and N200) in BD patients.

Several studies have reported P300 abnormalities among BD patients. Prolonged P300 latency in BD patients relative to healthy controls is the most consistent finding across studies (5, 7–10), although some studies found no differences between groups on this measure (11, 12). Comparisons of P300 peak amplitude between BD patients and controls have produced less consistent results. Some studies have found reduced P300 amplitude in BD patients relative to controls (7, 8, 11, 12), while others have found equivalent P300 amplitudes between BD patients and controls (5, 9, 10). One study found that P300 amplitude did not differ between a sample of patients suffering from first-episode affective psychosis (primarily BD) and healthy controls (12). Lastly, reduced P300 amplitude has been reported in BD patients who were in remission for six months, suggesting that this measure indexes a relatively stable deficit that remains even following an extended euthymic period (13). That study found no evidence for abnormal P300 latency in BD patients in remission, indicating that patients may improve in this respect as symptoms remit.

Only two studies have examined the N100, P200, and N200 components in patients with BD. These ERPs precede the P300 in time and reflect earlier stages of information processing.
processing. Muir et al. (7) found N100 and N200 latency prolongation in BD patients relative to controls, with no differences found for P200 latency. The authors found no between-group differences in the amplitudes of those components in that study. Similarly, O’Donnell et al. (8) found that BD patients and healthy controls demonstrated similar peak amplitudes for the N100, P200 and N200 ERPs. However, no between-group latency differences were found for any of these components. Thus, it remains unclear whether early processing of auditory stimuli is disrupted in BD.

The interpretation of previous studies of auditory ERPs in BD is complicated by the possible effect of current mood symptoms, medication status, or comorbid psychiatric diagnoses on measures of component amplitude and latency. Few studies have compared auditory ERPs from BD patients who were euthymic at testing with those of patients who were symptomatic (i.e., manic or depressed). An exception is a study by Muir and colleagues (7), who reported no differences between manic, depressed, and euthymic subgroups of patients on the amplitude or latency of the N100, P200, N200, and P300. In addition, many BD patients also meet lifetime criteria for a substance use disorder (SUD) or anxiety disorder (14), both of which have been associated with P300 abnormalities (15). While some studies of auditory ERPs in BD have excluded patients with a history of a SUD (5, 8, 11, 16), others have not described patients’ histories of drug or alcohol abuse or dependence (7, 9, 10). We are unaware of any previous studies that have compared BD patients with and without a history of an anxiety disorder on measures of auditory ERPs.

Three previous studies found no relationship between P300 measures and medication status (i.e., medicated versus unmedicated) among BD patients (5, 7, 8, 10). Furthermore, Souza and colleagues (9) reported no significant correlation between antipsychotic medication dose (chlorpromazine equivalent) and P300 amplitude or latency among BD patients. However, O’Donnell et al. (8) reported that P200 latency was significantly prolonged in BD patients taking antipsychotic medications compared to unmedicated patients. The relationship between medication usage and other auditory ERPs (e.g., N200) in patients with BD currently is unclear.

A greater understanding of the relationship between changes in affect and ERP indices of cognitive functioning could improve our knowledge of the associations between neurobiological dysregulation and behavioral changes (17). Abnormalities in auditory ERPs have been identified as candidate endophenotypes for BD (4, 5, 18–20). To be considered an endophenotype for BD, a measure should be state-independent (21) and reflect the causes of the disorder, rather than its consequences or the effects of treatment (22). Furthermore, as a marker of risk for the development of BD, a putative endophenotype should be observable in BD regardless of history of other psychiatric disorders. In the present study, we investigated the impact of mood state on auditory ERP measures in BD patients by comparing patients who were euthymic at testing with those who exhibited active mood symptoms. We also investigated the relationship between demographic (years of education, estimated IQ) and clinical (age of illness onset, medication status, history of psychotic features, history of a comorbid SUD or anxiety disorder) variables and ERP measures.
Methods

Participants

Sixty-nine individuals with type I bipolar disorder (44 females) were recruited at the Indiana University School of Medicine Neuroscience Clinical Research Center in Indianapolis, IN. Patients were diagnosed using research modules of the Structured Clinical Interview for the DSM-IV (SCID; 23). Fifty-two (75%) were outpatients during the time of their participation, while 17 (25%) were inpatients. Fifty-two control subjects (28 females) were recruited from the community via an electronic newsletter. All participants were between 18 and 65 years of age and had completed grade-school level education. Exclusion criteria for all participants included a history of cardiovascular or neurological disease, a history of a head injury that resulted in loss of consciousness, or a first-degree relative with schizophrenia. For control participants, exclusion criteria included a history of substance abuse or dependence, a diagnosis of any current or past Axis I psychiatric illness, or current illegal drug use. Estimated IQ was obtained from most participants (n = 36 and n = 66 for controls and bipolar patients, respectively) using the Wechsler Abbreviated Scale of Intelligence (WASI; 24). The study was approved by the local institutional review board, and oral and written informed consent was obtained from all participants prior to the administration of any testing.

The clinical state of patients at the time of testing was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS; 25) and the Young Mania Rating Scale (YMRS; 26). BD patients were classified as “euthymic” (n = 20) if their total scores on the YMRS and MADRS at testing were ≤ 12 and ≤ 8, respectively, and “symptomatic” (n = 49) if their score on either measure exceeded those values. Scores less than 12 on the YMRS indicate euthymia (26), while scores greater than 8 on the MADRS correspond to the presence of “mild” depressive symptoms (27). The euthymic and symptomatic groups differed significantly on their scores on the YMRS and MADRS, but did not differ in their age of illness onset or illness duration (see Table 1).

Demographic information for each group is presented in Table 1. The groups did not differ on years of education, age, estimated IQ (Fs < 1.79, n.s.) or the proportion of females within each group (χ² = 1.33, n.s.). Information on prior episodes of psychosis was available for 68 BD patients. Eight euthymic BD patients and 18 symptomatic BD patients reported a prior psychotic episode. This difference was not significant (χ² = 0.04, n.s.).

Medication status was available for 62 patients. Of these, most (n = 48) were taking at least one psychotropic medication. The frequencies of different medication types for the symptomatic and euthymic patient groups are shown in Table 2. Thirty patients were taking more than one type of medication at testing. Fourteen patients (1 patient from the euthymic group and 13 from the symptomatic group) were unmedicated at testing. The mean (S.D.) withdrawal duration for the unmedicated group was 41.4 (63.0) days.

Several BD patients met diagnostic criteria for an additional current or past SUD or anxiety disorder (see Table 3). Of the euthymic BD patients, 8 had no history of a SUD or anxiety disorder, 8 met criteria for a current or past anxiety disorder, 2 met criteria for a current or...
past anxiety disorder, and 2 met criteria for both a current/past SUD and a current/past anxiety disorder. Among members of the symptomatic BD group, nineteen did not meet criteria for any other psychiatric diagnosis, 14 met criteria for a current or past SUD, 7 met criteria for a current or past anxiety disorder, and 9 met criteria for both a current/past SUD and a current/past anxiety disorder. The frequencies of the different SUD and anxiety disorder diagnoses among members of the BD group are listed below Table 3.

EEG data collection and processing

EEG was continuously recorded from the scalp using a 32-channel cap (10–20 system; Falk-Minow Services, Munich, Germany) with a nose reference. EEG was acquired using a Neuroscan SYNAMPS recording system (Neuroscan Inc., El Paso, TX) at 1000 Hz with a 0.10 Hz high-pass filter and a 200 Hz low-pass filter. Electrode impedances were maintained below 10 kΩ. During recording, 86 dB SPL tone pips were presented binaurally for 50 ms via Etymotic insert earphones. Subjects were instructed to respond by pressing a button with their left hand to 1500 Hz target tones which were interspersed randomly among 1000 Hz tones. Participants were exposed to a total of 500 tones (425 standard, 75 rare).

For offline analysis, EEG was segmented into 900 ms epochs with a 100 ms pre-stimulus baseline. A 24 Hz (24 dB/octave roll-off) low-pass filter was applied to the waveform of each epoch. The average value from the 100 ms baseline period was subtracted from all sample points in the epoch for baseline correction. Artifacts related to vertical eye movement were corrected using the algorithm of Gratton, Coles, and Donchin (28). Epochs containing voltage samples exceeding ± 100 μV at any recording site were excluded from further analysis. Epochs containing frequent standard and infrequent target tones were averaged separately. The N100 and P200 components were measured from the averaged response to standard tones, whereas the N200 and P300 components were measured from the averaged response to target tones. Peak latencies were measured at the electrode sites where the ERP had the largest amplitude averaged across all subjects. Amplitude measurements at that peak latency value for each subject were then obtained from all electrode sites. The latency windows for all components were defined relative to the onset of the stimulus. The latency of the N100 was scored at the largest negative value at Fz 80–150 ms post-stimulus. P200 latency was scored at the largest positive value at Cz within 175–275 ms. N200 latency was scored at the largest negative value at Fz within 175–275 ms. P300 latency was measured as the largest positive value at Pz within 280–600 ms post-stimulus. The peak amplitude of a component was measured as the mean of the maximally positive (P200, P300) or negative (N100, N200) voltage and the surrounding 20 data points (i.e., the maximal value ± 10 data points). One female symptomatic BD patient was excluded from the P300 analyses because her mean amplitude for this ERP was greater than three standard deviations above the mean for the symptomatic BD group.

Statistical analysis

ERP amplitude and latency were submitted to a one-way analysis of covariance (ANCOVA) with the factors group (3: control, euthymic BD, symptomatic BD) and sex (2: male, female), with participant age as a covariate. ERP component amplitudes were computed at the site at which they were maximal and compared between groups using ANCOVA. In
addition, amplitude measures were submitted to ANCOVA with the factors group (3), sex (2), and electrode site (5: Fz, FCz, Cz, CPz, and Pz), and participant age as a covariate, to investigate between-group differences in amplitude across electrode sites. We focused on midline sites to facilitate comparison between the present results and those presented in previous studies of ERPs in BD patients. For all analyses, post-hoc ANOVA or t-tests were used to clarify any significant main effects or interactions revealed by ANCOVA. Degrees of freedom were corrected using the Huynh-Feldt correction where appropriate. Hierarchical multiple regression was used to explore potential relationships between demographic and clinical data and ERP amplitude and latency measures after adjusting for the effects of age and sex. A two-tailed p value of ≤ .05 was used for significance testing.

Results

Behavioral performance

Response accuracy as percent correct was evaluated between the control, euthymic BD, and symptomatic BD groups using ANOVA. These analyses indicated that the groups did not differ significantly in terms of their ability to respond accurately to the target tones, F(2, 117) = 1.83, p = 0.17. Mean (S.D.) values for accuracy were 0.94 (0.08) for controls, 0.91 (0.18) for the euthymic BD group, and 0.89 (0.16) for the symptomatic BD group.

ERP components

N100—No main effect of group was found for N100 amplitude to frequent tones at Fz, F(2, 114) = 1.14, p = 0.33 (see Figure 1). There was a main effect of electrode site, F(1.57, 179.31) = 10.24, p < 0.001, and post-hoc ANOVAs indicated that the N100 was most negative at Fz and FCz (ps < 0.001). N100 latency did not differ among the groups, F(2, 114) = 1.59, p = 0.21.

P200—There was a main effect of group for P200 amplitude to frequent tones at Cz, F(2, 114) = 3.94, p = 0.02 (Figure 1). Follow-up t-tests indicated that the control group exhibited greater P200 amplitude at Cz than both the euthymic [t(70) = 2.23, p = 0.03] and symptomatic [t(99) = 2.61, p = 0.01] BD patient groups. The two patient groups did not differ on P200 amplitude [t(67) = 0.03, p = 0.98]. There was a significant main effect of electrode site for P200 amplitude, F(1.84, 210.67) = 3.25, p < 0.05, and pairwise comparisons confirmed that the amplitude of that component was largest at Cz (ps < 0.01). P200 latency did not differ significantly among the groups, F(2, 114) = 1.90, p = 0.15.

N200—N200 amplitude to target tones did not differ among groups at Fz, F(2, 114) = 1.20, p = 0.31 (Figure 2). There was a main effect of electrode site, F(1.65, 188.09) = 14.81, p < 0.001, and post-hoc pairwise comparisons indicated that N200 was most negative at Fz (ps < 0.005) across subjects. N200 latency did not differ significantly among the groups, F(2, 114) = 1.90, p = 0.15.

P300—P300 amplitude to infrequent target tones at Pz differed significantly among the groups, F(2, 113) = 6.89, p = 0.002 (see Figure 2). Post-hoc t-tests indicated that the control group exhibited greater P300 amplitude than the euthymic (p = 0.003) and symptomatic (p =
0.01) BD patient groups. The euthymic and symptomatic BD patient groups did not differ in terms of P300 amplitude, \( p = 0.12 \). There was a main effect of electrode site \( [F(2.03, 229.27) = 27.44, p < 0.001] \), and posthoc comparisons revealed that P300 amplitude was largest at Pz and smallest at frontal sites \( (p < 0.001) \). P300 latency did not differ between the groups, \( F(2, 113) = 1.53, p = 0.22 \).

### Comparisons between all BD patients and controls

To facilitate comparison between the results of the present investigation and those published previously, we collapsed both BD patient groups and compared them to control subjects on measures of auditory ERP amplitude and latency, as described above. The difference between BD patients and controls for P300 latency was significant at the trend level, \( F(1, 115 = 2.95), p = 0.09 \). The peak latency of the P300 ERP tended to be prolonged among BD patients relative to controls \([\text{control mean (S.D.) latency} = 380.35 (66.81) \text{ ms}, \text{patient mean (S.D.)} = 408.32 (74.51) \text{ ms}].\) Overall, BD patients exhibited lower amplitudes for P300 \( [F(1, 115) = 12.54, p = 0.001] \) and P200 \( [F(1, 116) = 8.01, p = 0.005] \). BD patients exhibited a trend toward prolonged P200 \( (p = 0.07) \) latency as well. No other comparisons approached significance.

### Relationships between ERP component measures and demographic and clinical measures

We conducted a hierarchical multiple regression analysis to examine the relationship between ERP amplitude and latency measures and demographic and clinical variables among BD patients. Patient age and sex were entered in the first step of the model. In the second step, demographic and clinical variables were entered using a stepwise procedure. Thus, the model tested the relationship between these variables and ERP measures after accounting for the effects of age and sex. The demographic and clinical variables tested with the model were years of education, estimated (WASI) IQ, age of illness onset, medication status at testing, history of psychotic features, and the presence of a current or past comorbid anxiety disorder, substance-use disorder, or both. Nominal variables (medication status, history of psychotic features, comorbid psychiatric diagnosis) were dummy-coded 0 or 1 prior to entry into the model, where 1 = “present” and 0 = “absent”. Among BD patients, total years of education predicted N100 amplitude after accounting for the effects of age and sex, \( \beta = -0.42, R^2 \text{ change} = 0.16, F(1, 54) = 11.61, p = 0.001 \). In addition, there was a significant relationship between a comorbid current or past anxiety disorder diagnosis and N200 latency, \( \beta = -0.38, R^2 \text{ change} = 0.14, F(1, 54) = 8.67, p = 0.005 \). BD patients who also met criteria for a current or past anxiety disorder exhibited shorter N200 latencies than patients without comorbid anxiety. Lastly, there was an effect of current/past comorbid anxiety on P300 latency, \( \beta = 0.32, R^2 \text{ change} = 0.10, F(1, 53) = 6.11, p = 0.02 \). P300 latency was prolonged in patients who met criteria for a current or past anxiety disorder relative to those who did not meet criteria for an additional anxiety-disorder diagnosis. No other demographic or clinical variables were related to amplitude or latency measures for any ERPs \((\text{all } p \text{ values n.s.})\).
**Discussion**

The present study examined the relationships between auditory ERP measures and mood state, recent medication use, and a current or past SUD or anxiety disorder diagnosis in patients with BD. P300 amplitude to target tones was reduced in both the symptomatic and euthymic BD patient groups relative to healthy control subjects, and BD patients showed prolonged P300 latency as well. The symptomatic and euthymic BD patient groups did not differ on P300 amplitude or latency. We also found that both patient groups exhibited reduced P200 amplitude to frequent tones compared to controls. A hierarchical multiple regression analysis indicated that a history of a comorbid anxiety disorder diagnosis may be associated with reduced N200 peak latency but increased P300 peak latency. We found no other effects of medication status, history of psychotic features, or history of a comorbid anxiety disorder or SUD on ERP measures in BD patients. Sex differences were noted on the amplitude measures of some ERPs, but did not interact with the effect of diagnosis. Overall, the present results suggest that auditory ERP measures obtained from BD patients are relatively insensitive to patients’ mood state, medication status, or history of psychotic features, but may be influenced by the presence of a comorbid anxiety disorder.

Previous reports have described reduced amplitude (7, 8, 11) and prolonged peak latency (5, 7–10) of the auditory P300 among BD patients compared to healthy comparison subjects. Our results replicate these findings, and suggest that the presence of an active mood disturbance at testing is unrelated to measures of P300 amplitude or latency among these patients. Other studies have reported no relationship between mood state at testing and P300 amplitude and latency in BD. Muir et al. (7) found that P300 amplitude and latency did not differ significantly across subgroups of depressed, non-depressed, and manic BD patients. In a separate study of 19 predominantly-euthymic BD patients, no relationship was found between ratings of mood state at testing and P300 amplitude or latency (9). A previous study from our group (8) found no relationship between YMRS and MADRS scores and P300 amplitude or latency measures, although relationships between mood ratings and other auditory ERPs were noted. Most recently, Schulze et al. (5) found no correlation between scores on self-report scales of mania and depression and P300 measures at Pz. Thus, the results of the present study are congruent with those of previous investigations and suggest that P300 amplitude and latency measures are insensitive to BD patients’ mood state at testing.

We found no relationship between patients’ medication status and ERP amplitude or latency, which echoes the results of previous studies (5, 7, 8, 10). However, the interpretation of this result is complicated by the small sample size (n = 14) of unmedicated patients in the present study, and the lack of control over the duration of the unmedicated periods. In addition, the present finding does not speak to the experimentally-manipulated effects of any one type of medication on ERP measures in BD patients. Future research with an experimental manipulation of medication is warranted to clarify the relationship between medication usage and auditory ERP measures in these individuals.

Similarly, P300 amplitude was unrelated to patients’ histories of a current or past SUD or anxiety disorder. Patients with a SUD show reduced P300 amplitude to target stimuli in
auditory “oddball” tasks relative to healthy control subjects (29–31). This represents a special challenge to the study of P300 in BD, as the lifetime co-occurrence of SUDs with that disorder has been estimated at approximately 60% across studies (14). Indeed, 48% of BD patients in the present study had a history of a SUD. Similarly, approximately 70% of BD patients suffer from comorbid anxiety disorders (14). Patients suffering from anxiety disorders demonstrate increased P300 amplitude relative to controls (15). Twenty-nine percent of the BD patients in the present study had a history of an anxiety disorder; of those, most (70%) had a diagnosis of current or past panic disorder (PD). Approximately 17% of BD patients meet criteria for a diagnosis of PD within their lifetime (32). Patients with PD, like patients with other anxiety disorders, exhibit an exaggerated P300 response to target tones in an auditory discrimination task (33). Our results indicated that the presence of a current or past SUD or anxiety disorder was unrelated to the amplitude of the P300 or any other auditory ERP among BD patients. In contrast, we found that the presence of a comorbid current or past anxiety disorder was associated with shorter N200 peak latency, but prolonged P300 peak latency, among BD patients. These findings may reflect the prevalence of PD among the BD patients in the present study who had a history of comorbid anxiety. Hanatani and colleagues (34) found that N200 peak latency was reduced among PD patients relative to healthy controls, but other similar studies did not find this relationship (35, 36). Similarly, peak P300 latency has been shown to be delayed in PD patients relative to healthy controls (33, 36), although other investigations did not report such differences (34, 35). Because the number of patients with a non-PD comorbid anxiety disorder was relatively small in the present study, it is unclear whether the present results may generalize to the larger population of BD patients who also suffer from an anxiety disorder. Additional research conducted with larger, more diverse samples of BD patients with an anxiety disorder will improve our understanding of the unique contributions of those diagnoses to differences in auditory ERP measures.

BD patients are impaired on neuropsychological tests of attention (for a review, see 37). The disruptions in P300 amplitude and latency displayed by BD patients in the present study are consistent with the theorized relationship between this ERP and processes related to attention and processing speed (3). Prolonged P300 latency was noted in the entire sample of patients in the present study, and is the most consistent finding across studies of this component in BD (5, 7–10). Prolonged P300 latency is believed to reflect deficits in attentional mechanisms and impairments in processing speed (38). The present results support the hypothesis that BD patients exhibit a trait disturbance in neurophysiological processes related to attention.

We found evidence that earlier processing of auditory information is disrupted in BD as well. P200 amplitude to frequent, non-target tones was reduced among both BD patient groups relative to controls. These findings contrast with those of previous studies of auditory processing in BD which found no difference between patients and controls on P200 amplitude (7, 8). The P200 is an exogenous ERP that is elicited automatically by auditory stimuli, but which is sensitive to alterations of the attentional demands of an auditory task (39–41). P200 amplitude is minimal when subjects listen passively to tone stimuli, but increases when subjects must discriminate between target and non-target tones. It has been demonstrated previously that patients with schizophrenia exhibit reduced P200 amplitude in
response to frequent tones presented during an auditory discrimination task (7, 8, 41, 42). The similar disruption exhibited by BD patients in the present study suggests that these individuals, like patients with schizophrenia, may be similarly impaired in their ability to allocate attentional resources when discriminating between auditory stimuli.

Reduced P300 amplitude is a robust finding among patients with schizophrenia (6, 43–45). Abnormalities in P300 or other auditory ERP measures may represent an underlying genetic vulnerability for psychotic disorders in general rather than susceptibility to a specific diagnostic category (5, 6). While BD and schizophrenia have been traditionally conceptualized as clinically discrete illnesses, the presence of mood disturbances in schizoaffective disorder, and of psychotic symptoms in BD, suggest that these disorders may share common biological disturbances. In addition, twin and family studies suggest that BD, schizoaffective disorder, and schizophrenia may share genetic risk factors (46). Several gene loci have been identified as common risk factors for both BD and schizophrenia, including DISC1, NRG1 and COMT (46). Specific genetic susceptibility loci, however, have not been replicated across studies and some have suggested that biomarkers or endophenotypes may be more closely associated with genetic variations than clinical diagnoses (6). P300 is a promising candidate endophenotype for BD and schizophrenia, since it is sensitive to both disorders and the deficit persists across changes in clinical state. Additionally, P300 measures appear to be heritable. Twin and family studies indicate that P300 amplitude has a heritability of about 60%, and that P300 latency has a heritability of about 51% (47). Moreover, a number of preliminary reports have associated P300 with specific gene effects, including COMT and DISC1 (6).

The present study provides further support for auditory P300 amplitude as a candidate endophenotype for BD, since that measure appeared to be relatively insensitive to differences in mood state, medication status, or comorbid conditions. Our results indicated that P300 latency may be sensitive to the presence of a comorbid anxiety disorder in BD patients, but more research is warranted in this area. It is important to note that P300 alterations are not specific to BD, since similar changes have been observed in schizophrenia. With respect to ERP components, N100 amplitude appears to more likely to differentiate these two disorders. N100 amplitude in the present study was unaffected by BD, consistent with previous studies of this component (8). In contrast, auditory N100 amplitude is usually reduced in schizophrenia (41, 48, 49). The present data does not suggest that bipolar patients with a history of psychotic features show a reduced N100 component. Thus, P300 deficits are common to both BD and schizophrenia, and may reflect common genetic vulnerabilities; while N100 amplitude reduction may be specific to schizophrenia.

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References


Figure 1.
Grand averaged ERPs at Fz and Cz following frequent, non-target tones in control subjects, euthymic BD patients, and symptomatic BD patients.
Figure 2.
Grand averaged ERPs at Fz and Pz following infrequent, target tones in control subjects, euthymic BD patients, and symptomatic BD patients.
### Table 1

<table>
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<th>Control</th>
<th>Euthymic BD</th>
<th>Symptomatic BD</th>
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<tr>
<td>N</td>
<td>52</td>
<td>20</td>
<td>49</td>
<td>-</td>
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<tr>
<td>Sex (M:F)</td>
<td>24:28</td>
<td>8:12</td>
<td>17:32</td>
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<td>Age in Years (S.D.)</td>
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<td>42.8 (9.8)</td>
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<td>Years of Education (S.D.)</td>
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<td>14.1 (1.8)</td>
<td>13.0 (2.7)</td>
<td>N.S.</td>
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<tr>
<td>WASI Est. IQ (S.D.)</td>
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<td>107.4 (13.9)</td>
<td>100.0 (16.5)</td>
<td>N.S.</td>
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<td>Age at Onset (S.D.)</td>
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<td>23.9 (9.1)</td>
<td>N.S.</td>
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<tr>
<td>Illness duration (years) (S.D.)</td>
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<td>18.5 (11.1)</td>
<td>N.S.</td>
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<tr>
<td>YMRS score (S.D.)</td>
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<td>18.0 (10.4)</td>
<td>&lt; .001</td>
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<td>MADRS score (S.D.)</td>
<td>-</td>
<td>3.0 (2.7)</td>
<td>16.3 (11.4)</td>
<td>&lt; .001</td>
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### Table 2

Incidence of Medication Types among BD Patient Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Euthymic</th>
<th>Symptomatic</th>
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<td>Atypical antipsychotic</td>
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<td>20</td>
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<td>Typical antipsychotic</td>
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<td>3</td>
</tr>
<tr>
<td>Lithium</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Total unmedicated</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Total medicated</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Total unknown</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 3
Frequency of Current or Past Substance Use or Anxiety Disorders Among the BD Patient Groups.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Euthymic</th>
<th>Symptomatic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No SUD or Anxiety Disorder</td>
<td>8</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Current/past SUD Only</td>
<td>8</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Current/past Anxiety Disorder Only</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>SUD and Anxiety Disorder (current or past)</td>
<td>2</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

Note: BD patients identified as “Current/past SUD Only” met diagnostic criteria for the following disorder(s): past alcohol abuse (3); past alcohol dependence (9); current marijuana abuse (1); past marijuana abuse (3); past marijuana dependence (2); past cocaine dependence (5); past opioid dependence (1); past sedative dependence (1); past stimulant dependence (2); past hallucinogen dependence (1).

BD patients identified as “Current/past Anxiety Disorders Only” met DSM-IV diagnostic criteria for the following disorder(s): past post-traumatic stress disorder (PTSD, 1); past panic disorder (PD, 2); current PD (3); current obsessive-compulsive disorder (OCD, 1); current social anxiety disorder (1); agoraphobia (1).

BD patients identified as “SUD and Anxiety Disorder (current or past)” met diagnostic criteria for the following disorder(s): past alcohol dependence (7); current alcohol abuse (1); past marijuana abuse (1); past cocaine dependence (4); past opioid dependence (1); past polysubstance dependence (1); past MDMA dependence (1); current PD (6); past PD (3); past OCD (4); past social anxiety disorder (3); current agoraphobia (1).